REMARKS

This application has been amended in a manner that is believed to place it in condition for allowance at the time of the next Official Action.

Claims 44, 49-50 and 91-104 are pending in the present application. Claim 44 has been amended. Support for amended claim 44 may be found in the present specification at page 1, line 30 to page 2, lines 35. New claims 91-104 have been added. Support for new claims 91-104 may be found in the original claims and generally throughout the specification. Claims 1-43, 45-48 and 51-90 have been canceled.

In the outstanding Official Action, claims 44, 46, 47, 49-51, 53-55, 60, 61, 88-90 were rejected for allegedly not satisfying the enablement requirement. This rejection is respectfully traversed.

In imposing the rejection, the Official Action alleges that the present disclosure does not teach how to make and use the claimed invention, or that the claims MD-APCs exist as a single phenotype. In addition, the Official Action holds that how one would interpret the present disclosure would be within the purview of experts in the field and not attorneys.

At this time, the Examiner's attention is respectfully directed to the Declaration by Dr. Michael Lotze. Applicants believe that the Declaration provides further evidence that the present disclosure is enabling for the claimed invention.

Indeed, the specification teaches from the outset that the claimed MD-APCs relate to new antigen presenting cells (page 1, lines 1-5; and page 1, line 30 to page 2, lines 35). Moreover, the present specification teaches that the novel MD-APCs may be identified by their antigen presenting capabilities and their phagocytic properties.

The antigen presenting capabilities of the MD-APCs may be determined by methods such as immunofluorescence staining and flow cytometry analysis (page 5, lines 1-6 and page 5, lines 18-31). In the present specification at page 5, lines 18-29, the characteristics of the claimed MD-APCs are exemplified.

Contrary to the teachings of the present specification, the Office Action interprets the characteristics of the claimed MD-APCs as indicating a mixed cell population. The Official Action believes that the disclosure at page 5 indicates that only 10% of the claimed cells express CD14, only 10% of the claimed cells need express CD64, only 30% of the claimed cells express CD80, and that only 30% of the claimed cells express CD80.

However, applicants submit that this interpretation is incorrect. The passage at page 5, lines 30-31 plainly teaches that the data relates to the immunofluorescence and flow cytometry analysis described in the specification at page 3, lines 14-21; page 4, lines 1-7; and page 5, lines 1-6.

Therefore, a relatively low percentage value on page 5 merely suggests that the already low expression of the antigen in question was not detected for all cells; or, in the case of phagocytosis, that, not all of the cells will ingest yeast particles in the time allotted for the test. Moreover, it would be expected by a person skilled in the art that the level of expression of the antigens would vary to some degree among the cells of a given population. That is, the same type of cell may express different levels of antigen depending upon the cell's development or physiological state. Thus, the level observation that the antigen expression may vary to some degree from one MD-APC to the next does not indicate a mixed cell population. Applicants believe that this is also supported by the declaration by Dr. Lotze.

Moreover, while the identification of the standards used in the immunofluorescence staining and flow cytometry analysis studies are not provided in the present application, the set of values and the relative magnitudes of those values in comparison to one another are still significant to one skilled in the art when characterizing the new phenotype. Applicants believe that this is also supported by the declaration by Dr. Lotze.

Table 1 illustrates the percentage yield of the cells in a culture over a time period of 4, 7, and 11 days. When taken in context with the present application, the yield relates to the

number of MD-APCs that survive over the indicated time periods. It does not indicate that other types of phenotypes are present.

Table 2 relates to the phenotypic analysis of the MD-APCs as determined by their immunofluorescence profile analysis. As the Examiner is aware, conventional macrophages do not normally express CD 83, whereas mature dendritic cells do express CD 83. In view of the absence of any detectable signal for CD 83 for the claimed MD-APCs as shown in Table 2, it is believed that this indicates that the MD-APCs are not conventional mature dendritic cells, and do not contain such cells in any significant proportion.

As to the CD 14/CD 64 values shown in Table 2, the values are too low to indicate that a large number of conventional macrophages are present in the culture. In particular, the Examiner's attention is respectfully directed to the HLA-DR value. As the Examiner is aware, the relatively high expression of HLA-DR is indicative of a good antigen-presenting cell, i.e., more like dendritic cells and less like macrophages.

Thus, the data in Table 2 is consistent with a novel, discrete and single cell type. The data does not support the theory that the cells comprise a mixed population of mature dendritic cells and conventional macrophages. Applicants believe that this is also supported by the declaration by Dr. Lotze.

Table 3 shows the percentage of phagocytic MD-APCs after the MD-APCs have been cultured with yeast for a set period

of time. As to the number of yeast particles that are phagocytosed, Table 3 shows percentage of MD-APCs that phagocytose 0 yeast particles; 1-5 yeast particles; 6-10 yeast particles; and > 10 yeast particles per the allotted time of the study. The fact that not all of the MD-APCs phagocytose the fixed yeast relates to the parameters of the test in that the MD-APCs may not come in to contact or phagocytose all of the fixed yeast that are present in the allotted time of the study.

Table 3 is indicative of a new cell type. In that table, applicants note that the two columns of data add up to 100%. A homogeneous population of conventional macrophages subjected to the same testing conditions would be expected to show about 40% of the macrophages ingesting no yeast particles after three hours, and about 60% ingesting from one to five yeast particles over that time same time period. In other words, Table 3 indicates that the claimed MD-APCs exhibit even stronger phagocytic properties than conventional macrophages.

A mixed population of mature dendritic cells and conventional macrophages would be expected to shift the percentages in Table 3 toward a cell culture that would phagocytose zero yeast particles. This stands in contrast to the results obtained with the claimed MD-APCs. As a result, the data in Table 3 is consistent with a novel cell type. As a result, the data again does not support the existence of a mixed population of mature dendritic cells and conventional macrophages.

Applicants believe that this is also supported by the declaration by Dr. Lotze.

Table 4 directly compares the MD-APCs with dendritic cells. Dendritic cells have been described as FC receptor negative, poorly adherent and non-phagocytic cells, possessing only a small number of lysosomes. In contrast, the MD-APCs show a high adherence capacity, exhibit a high phagocytic and processing activity, and express high level HLA-DR membrane antigens. The MD-APCs are also positive for CD54, CD58, CD80, and CD86 membrane antigens. A mixed population of mature dendritic cells and conventional macrophages would shift the results of Table 4.

Table 5 is directed to the phenotypic characterization of MD-APCs recovered after 6 days of culture and confirm the characteristics of the MD-APCs as discussed above.

In imposing the rejection, the Office Action states that the present disclosure does not contain raw data but rather applicant's analysis of "uncontrolled data" as set forth in the present specification and Tables 1-5. As a result, the Office Action disregards applicant's analysis that the data supports a single, discrete cell type.

However, the Examiner is respectfully reminded that any assertion by the Patent Office that the enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubt so expressed.

As a matter of law, the expressed teaching of the patent specification cannot be controverted by mere speculation and unsupported assertions on the part of the Patent Office. As stated by the Court of Customs and Patent Appeals in the case of *In re Dinh-Nguyen and Stanhagen,* 181 USPQ 46 (CCPA 1974):

> Any assertion by the Patent Office that the enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubt so expressed. 181 USPQ at 47.

Such a standard must be applied with great care when the Examiner's conjecture is contrary to the teachings of the specification.

In an effort to support the position that the present disclosure does not support the existence of a single, discrete cell type, the Official Action cites to Boyer et al., Chaperot et al., and Paul et al.

However, contrary to the position taken by the Office Action, these publications actually support the patentability of the claimed MD-APCs. BOYER et al show the results of the uptake of the yeast by MAC-DCs, which correspond to the claimed MD-APCs (Boyer et al, pg 752, second column, second paragraph, titled, "*Generation of MAC-DC with GM-CSF*"). BOYER et al. compare the ability of macrophages and the claimed MD-APCs ability to capture and phagocytose yeast (Figures 2, 3 and 4). In contrast to the macrophages, a large number of yeast was found to be phagocytosed by the claimed MD-APCs. No single macrophage is able to

phagocytose more than 15 yeast whereas about 40% of the MD-APCs did (Figure 3).

CHAPEROT et al show ability of MD-APCs to stimulate T cell proliferation as opposed to monocytes and macrophages. CHAPEROT et al refer to the MD-APCs as macrophages (Mø). The culture and purification conditions utilizing IL-13 outlined on page 1668. As to the results, Figure 2 shows a greater ability of MD-APCs to stimulate T cell proliferation than monocytes and macrophages, the level of response being 3 to 20 fold higher at 0.5/1 APC/T lymphocyte ratio.

As to the excerpt from *Fundamental Immunology* by Paul, the excerpt shows a cytokine-driven differentiation of a monocyte into a mature dendritic cell. Contrary to the assertions of the Office Action, the excerpt does not follow the teachings of the present disclosure. Applicants believe that the excerpt merely provides a generic overview as to the differentiation of a monocyte into a mature dendritic cell. Indeed, upon reviewing the articles cited in support of this passage (199 and 275), neither article teaches the use of IL-13. Rather, the articles focus on the use of IL-4 and do not disclose or suggest the method for producing the MD-APCs disclosed in the present specification. As a result, it is believed to be apparent that the cells are directed to cell types that are distinct from the claimed invention for the Examiner's convenience. The articles are enclosed with this amendment.

As a result, applicants believe that the excerpt fails to support the contentions of the Patent Office that the present disclosure does not satisfy the enablement requirement.

The Official Action also contends that, if the novel MD-APCs are produced using IL-13, then a question would arise as to whether the claims are novel in view of Piemonti et al., "IL-13 supports differentiation of dendritic cells from circulating precursors in concert with GM-CSF," *Eur. Cytokine Netw.*, Vol. 64, No. 4, July-December 1995, pp. 245-252. However, the teaching of the IDM patent specification is quite clear that the monocytes are collected by apheresis and are cultured in a non-adhered state, e.g., in hydrophobic bags (see page 10, lines 10-12; page 12, lines 20-21; and page 15, lines 23-24).

This stands in contrast to Piemonti et al, wherein monocytes were plated prior to culturing (see p. 246. left-hand column "[c]ells were cultured for 7 days at 5 x 105/ml in 6-well tissue culture plates..."; and p. 247, left-hand column, "[a]fter 7 days cell recovery for both cytokine combinations was usually 50-70% of the cells originally plated"). Those skilled in the art know that the utilization of adhered monocytes leads to a cell type different than that obtained using non-adhered monocytes as set forth in the claimed invention. Applicants believe that this is also supported by the declaration by Dr. Lotze.

As to producing the claimed the MD-APCs, the Official Action argues that the specification provides just a single

method comprising a single combination of reagents for producing the single cell "asserted" by applicants. As a result, the Official Action states that the limited disclosure does not support the claimed product as broadly claimed.

However, the specification teaches at least two ways to produce the MD-APCs in that the MD-APCs can be obtained by differentiating blood monocytes in vitro, in the presence of lymphocytes, GM-CSF and at least one ligand having a receptor on the surface of monocytes. (present specification, page 10, line 3 to page 14, line 14). The "at least one ligand having a receptor on the surface of monocytes" may be chosen from histamine or an agonist of a histamine receptor (H1 in action) in combination with a H2 antagonist such as cimetidine; or IL-13.

Moreover, as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Failure to disclose other methods by which the claimed invention may be made does not render a claim invalid under 35 U.S.C. 112. *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1533, 3 USPQ2d 1737, 1743 (Fed. Cir.), *cert. denied*, 484 U.S. 954 (1987). As noted above, the Office Action acknowledges that the present specification teaches a method for making and using the claimed MD-APCs.

As to the scope of the claims, claims 44, 49-50 and 91-104 are directed to monocyte-derived antigen-presenting cells (MD-APCs). While the scope of each claim may vary, the claimed MD-APCs are all characterized to some extent by their phagocytic and antigen-presenting properties. As noted above, the tests and methods for determining the phagocytic and antigen-presenting properties of claimed MD-APCs are plainly described in the in the present specification. As a result, applicants believe that the claimed MD-APCs are fully supported by the claimed invention.

Thus, in view of the present specification, applicants believe that one of ordinary skill in the art would be able to make and use the novel, discrete cell type taught in the present disclosure.

Claims 44, 46, 47, 49-51, 53-55, 60, 61, 88 and newly-added claims 89 and 90 were rejected under 35 USC §112, first paragraph, for allegedly introducing new matter into the specification.

In imposing the rejection, the Official Action alleged that the present disclosure did not support the phrase "said MD-APCs having, when compared with monocyte derived macrophages prepared in the presence of GM-CSF only, higher phagocytic properties of formalin fixed yeast and higher ability for stimulation of allogenic T lymphocytes".

However, the present disclosure discusses the tests used to determine the phagocytic and antigen presenting

properties in detail beginning on page 3 of the present specification. Moreover, pages 1-3 in the present specification discuss the attributes of conventional macrophages, dendritic cells and the claimed MD-APCs. In doing so, the specification implicitly compares and contrasts the claimed MD-APCs with dendritic cells and conventional macrophages.

In addition, the Official Action alleged that the use of IL-13 as set forth in claim 89 was not supported by the present disclosure. The Official Action stated that the recitations directed to IL-13 were only disclosed in specific examples and as a result, the claim 89 introduces new matter into the present disclosure.

While claim 89 has been canceled, applicants noted that claims 97-103 are directed to MD-APCs that are produced by differentiating non-adhered blood monocytes in vitro, in the presence of GM-CSF, and IL-13. As acknowledged by the Examiner, IL-13 is exemplified in Figure 1 and also discussed on page 14 in the present specification. As a result, IL-13 is clearly contemplated and supported as a ligand that can be used to produce the claimed MD-APCs.

Thus, in view of the above, applicants believe that the new matter rejection is improper and must be withdrawn.

Claims 14-22 and 27-28 were rejected under 35 USC §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter

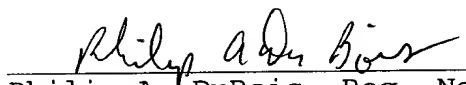
which applicants regard as the invention. Applicants believe that the present amendment obviates this rejection.

As noted above, claims 47, 89 and 90 have been cancelled. As a result, applicants believe that this rejection has been rendered moot.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

YOUNG & THOMPSON



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APPENDIX:

The Appendix includes the following items:

- executed Rule 132 Declaration of Dr. Michael T. Lotze

- Sallusto et al. publication "Efficient presentation of soluble antigen by cultured human dendritic cells is maintained by granulocyte/macrophage colony-stimulating factor plus interleukin 4 and downregulated by tumor necrosis factor", J.Exp.Med., Vol. 179, April 1994

- Romani et al. publication "Proliferating dendritic cell progenitors in human blood", J.Exp.Med., Vol. 180, July 1994.